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An efficient synthesis of cycloalkane-1,3-dione-2-spirocyclopropanes from 1,3-cycloalkanediones using (1-aryl-2-bromoethyl)dimethylsulfonium bromides: application to a one-pot synthesis of tetrahydroindol-4(5*H*)-one

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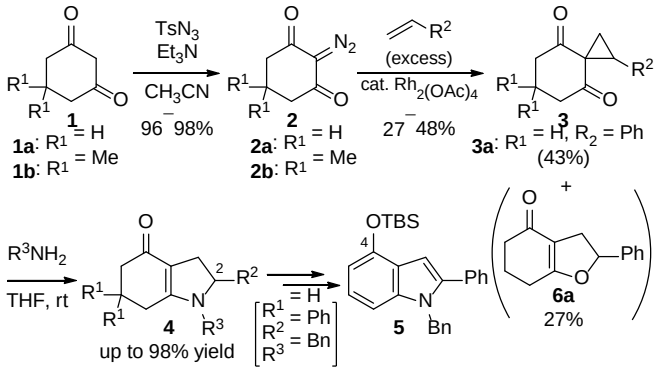
ABSTRACT

An efficient synthesis of cyclohexane- and cyclopentane-1,3-dione-2-spirocyclopropanes from 1,3-cycloalkanediones using sulfonium salts was achieved. The reaction of 1,3-cycloalkanediones with (1-aryl-2-bromoethyl)dimethylsulfonium bromides and powdered K_2CO_3 in EtOAc provided the corresponding spirocyclopropanes in high yields. Furthermore, a one-pot synthesis of tetrahydroindol-4(5*H*)-one from 1,3-cyclohexanedione was achieved by using the present protocol and a sequential ring-opening cyclization of spirocyclopropane with a primary amine.

Doubly activated cyclopropanes represent versatile intermediates for the synthesis of a variety of carbo- and heterocyclic compounds.[1] In this context, a ring-opening cyclization reaction of doubly activated cyclopropanes with primary amines is one of the most powerful methods for the construction of pyrrole skeletons.[2] Very recently, we reported the first example of the formation of indole skeletons by employing the ring-opening cyclization of spirocyclopropanes. The reaction of cyclohexane-1,3-dione-2-spirocyclopropanes **3**, derived from 1,3-cyclohexanediones **1**, with primary amines proceeded smoothly at room temperature to give high yields of tetrahydroindol-4(5*H*)-ones **4**, one of which was easily converted to 4-hydroxyindole **5** (Scheme 1).[3] This procedure provides a useful method for the synthesis of 4-hydroxyindoles. However, there is still a need for improvement in the yields of spirocyclopropanes **3** in Rh(II)-catalyzed cyclopropanation[4–6] with 2-diazo-1,3-cyclohexanediones **2** (27–48% yields). The reaction of alkenes and diazo substrates derived from active methylene compounds in the presence of an Rh(II) catalyst is widely employed for the synthesis of a variety of doubly activated cyclopropanes. In the case of the preparation of spirocyclopropanes, the Rh(II)-catalyzed reaction also produced several cyclopropanes easily but in low yield and was accompanied by a large amount of by-products. For example, the reaction of an excess amount of styrene with 2-diazo-1,3-cyclohexanedione (**2a**) using a catalytic amount of $Rh_2(OAc)_4$ gave spirocyclopropane **3a** in 43% yield and tetrahydrobenzofuran-4(5*H*)-one **6a**[7] as a by-product in 27% yield (Scheme 1).[6] Furthermore, this protocol is a two-step conversion from 1,3-cyclohexanediones **1** and requires a potentially explosive diazo compound. These drawbacks led us to develop a concise and practical route to spirocyclopropanes **3** from 1,3-cyclohexanediones **1**. Herein, we report an efficient synthesis of 1-arylspiro[2.5]octane-4,8-diones **3** using (1-aryl-2-bromoethyl)dimethylsulfonium bromides **7** (Scheme 2).



Scheme 1. Synthesis of 4-hydroxyindole **5** employing a ring-opening cyclization of cyclohexane-1,3-dione-2-spirocyclopropane **3** with amine.

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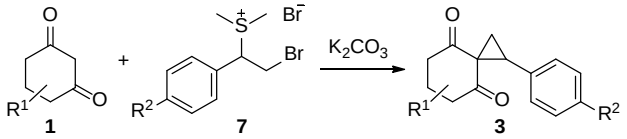
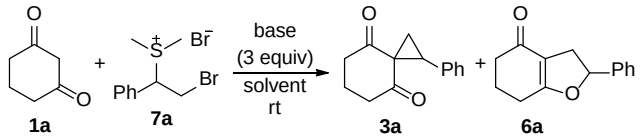


Scheme 2. Syntheses of spirocyclopropanes **3** from 1,3-cyclohexanediones **1** and sulfonium salts **7**.

The reaction of active methylene compounds such as malonate and β-ketoester with sulfonium salts has been established[8–10] as an alternative approach to doubly activated cyclopropanes. Recently, Chandrasekaran and Gopinath reported that the reaction of 2,4-pentanedione with (2-bromo-1-phenylethyl)dimethylsulfonium bromide (**7a**) and K_2CO_3 in CH_2Cl_2/H_2O (1:1) gave the corresponding cyclopropane in 65% yield.[9] Lu and co-workers applied this reaction to a cyclic alkanedione system, in which the reaction was conducted using DBU in DMSO, although the yield was very low.[10] At the outset, we examined the reaction of 1,3-cyclohexanedione (**1a**) with sulfonium salt **7a** for the synthesis of 1-phenylspiro[2.5]octane-4,8-dione (**3a**) according to Chandrasekaran's procedure (Table 1, entry 1). The reaction of **1a** with 1.5 equiv of **7a** using K_2CO_3 in CH_2Cl_2/H_2O (1:1) at room temperature provided **3a** in 30% yield. To enhance the yield of **3a**, we then screened other solvents. Switching the solvent to CH_2Cl_2 made the reaction messy to give tetrahydrobenzofuran-4(*5H*)-one **6a** in 6% yield without **3a** (entry 2). The use of CH_3CN, ^{i}PrOH, and THF resulted in low yields of **3a** (7–14% yields, entries 3–5). We considered that the poor solubility of sulfonium salt **7a** led to low product yields. With the highly polar solvents DMF and DMSO, spirocyclopropane **3a** was obtained in 26% and 35% yields, respectively, along with **6a** in 28% and 23% yields, respectively (entries 6 and 7). Surprisingly, the reaction in EtOAc proceeded smoothly to completion within 1.5 h and gave **3a** in 81% yield (entry 8), although **7a** is almost insoluble in EtOAc. A survey of bases revealed that K_2CO_3 was the optimal base for this transformation (entry 8 vs entries 9 and 10). To our delight, the use of powdered K_2CO_3, which was finely ground in a mortar, instead of granular K_2CO_3 increased the product yield of **3a** (92% yield, entry 11).

Table 1

Reaction of 1,3-cyclohexanedione (**1a**) with sulfonium salt **7a**[a]



(1.5 equiv)

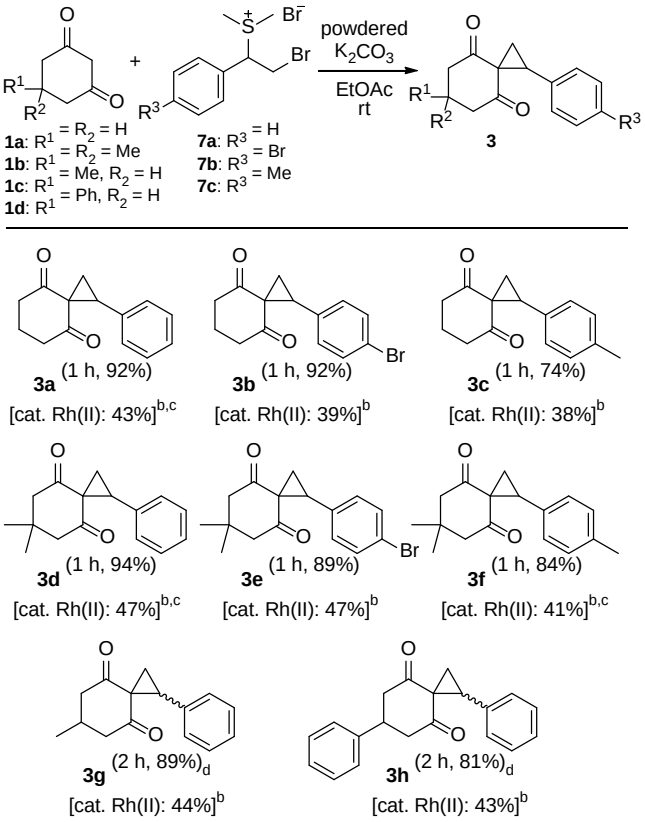
entry	base	solvent	time (h)	yield (%)[b] **3a**	**6a**
1	K_2CO_3	CH_2Cl_2/H_2O (1:1)	8	30	trace
2	K_2CO_3	CH_2Cl_2	24	trace	6
3	K_2CO_3	CH_3CN	9	14	trace
4	K_2CO_3	^{i}PrOH	20	9	9
5	K_2CO_3	THF	24	7	trace
6	K_2CO_3	DMF	4	26	28
7	K_2CO_3	DMSO	2	35	23
8	K_2CO_3	EtOAc	1.5	81	trace
9	^{t}BuOK	EtOAc	24	trace	trace
10	DBU	EtOAc	0.5	20	7
11	K_2CO_3[c]	EtOAc	1	92	trace

[a] All reactions were performed on a 0.5 mmol scale.
[b] Isolated yield.
[c] Powdered K_2CO_3 was used.

With the optimal conditions in hand,[11] we investigated the scope of the reaction of a variety of 1,3-cyclohexanediones **1a–d** with several sulfonium salts **7a–c** prepared from styrene derivatives and bromodimethylsulfonium bromide[12,13] (Table 2). The reaction of **1a** with **7b** and **7c** bearing *p*-bromo or *p*-methyl substituents on the benzene ring provided the corresponding spirocyclopropanes **3b** and **3c**[14] in 92% and 74% yields, respectively. High yields of **3d–f**[14] (84–94% yields) were consistently obtained in the reaction of dimedone (**1b**) with **7a–c**. The reaction of 5-methyl- and 5-phenyl-1,3-cyclohexanediones (**1c** and **1d**) with **7a** afforded diastereomeric mixtures (ca. 1:1) of spirocyclopropanes **3g** and **3h** in 89% and 81% yields, respectively. We then examined the Rh(II)-catalyzed cyclopropanation of the corresponding styrene derivatives with 2-diazo-1,3-cyclohexanediones derived from **1a–d**, and the yields are shown in square brackets in Table 2. In all cases, the yields of **3a–h** (38–47% yields) were lower than those obtained by the reactions of **1** and **7**.

Table 2

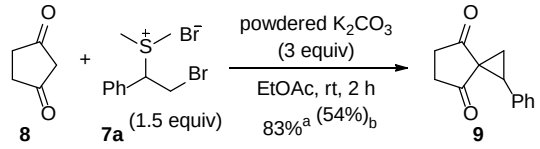
Reaction of 1,3-cyclohexanediones **1a–d** with sulfonium salts **7a–c**[a]



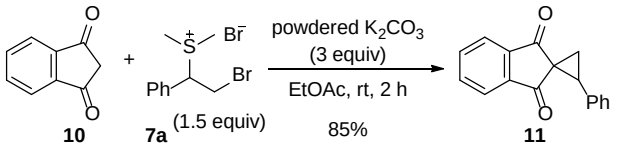
[a] All reactions were performed on a 0.5 mmol scale with 1.5 equiv of sulfonium salts **7a–c** and 3 equiv of powdered K_2CO_3 in EtOAc.
[b] Yields in square brackets were obtained in the reactions of large amounts of the corresponding styrene derivatives with 2-diazo-1,3-cyclohexanediones derived from **1a–d** in the presence of 1 mol % of $Rh_2(OAc)_4$.
[c] Ref. 3.
[d] The products **3g** and **3h** were isolated as a diastereomeric mixture (ca. 1:1).

We next turned our attention to the reaction of 5-membered carbocycles with sulfonium salt **7a** (Scheme 3). The reaction of 1,3-cyclopentanedione (**8**) with 1.5 equiv of **7a** using powdered K_2CO_3 in EtOAc provided the corresponding spirocyclopropane **9** in 83% yield (determined by ^{1}H NMR analysis).[15,16] The use of 1,3-indanedione (**10**) as an active methylene compound afforded

spirocyclopropane **11**[17] in 85% yield. Thus, the present protocol can be applied to the synthesis of spiro[2.4]heptane compounds.

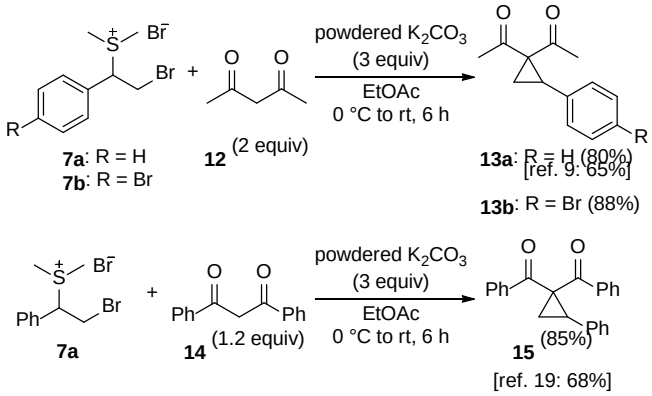


[a] Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard.
[b] Isolated yield.



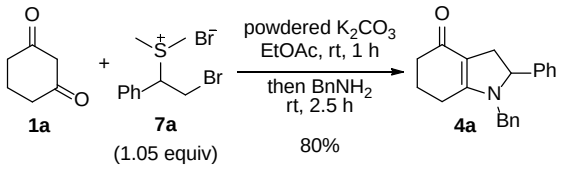
Scheme 3. Reactions of 1,3-cyclopentanedione (**8**) and 1,3-indanedione (**10**) with sulfonium salt **7a**.

To expand the scope of the present protocol, we then examined the reaction with acyclic 1,3-diones (Scheme 4). The reaction of sulfonium salts **7a** and **7b** with 2 equiv of 2,4-pentanedione (**12**) using powdered K_2CO_3 in EtOAc provided the corresponding doubly activated cyclopropanes **13a**[9] and **13b**[18] in 80% and 88% yields, respectively. The use of 1,3-diphenyl-1,3-propanedione (**14**) as an acyclic 1,3-dione afforded cyclopropane **15** in 85% yield.[19] Since the yields of **13a** and **15** were higher than those reported in literatures,[9,19] these results clearly demonstrate that the combination of powdered K_2CO_3 as a base and EtOAc as a solvent is also effective for the reaction with acyclic 1,3-diones.



Scheme 4. Reactions of sulfonium salts **7a** and **7b** with acyclic 1,3-diones **12** and **14**.

Finally, we investigated a one-pot conversion from 1,3-cyclohexanedione (**1a**) to tetrahydroindol-4(5*H*)-one **4a** (Scheme 5). In our previously reported ring-opening cyclization reaction of spirocyclopropane with a primary amine (Scheme 1), obvious solvent effects were not observed.[3] The reactions were almost the same in CH_2Cl_2, CH_3CN, THF, and toluene. These observations indicate that EtOAc would be usable in this ring-opening cyclization. After the reaction of **1a** with 1.05 equiv of **7a**[20] in EtOAc for 1 h, 2 equiv of benzylamine was directly added to the reaction mixture. The desired ring-opening cyclization reaction proceeded smoothly at room temperature to afford **4a** in 80% yield from **1a**.



Scheme 5. One-pot synthesis of tetrahydroindol-4(5*H*)-one **4a** from **1a**.

In conclusion, we have developed an efficient procedure for the synthesis of cyclohexane-1,3-dione-2-spirocyclopropanes from 1,3-cyclohexanediones using sulfonium salts. The reaction of 1,3-cyclohexanediones with (1-aryl-2-bromoethyl)dimethylsulfonium bromides and powdered K_2CO_3 in EtOAc provided the corresponding spirocyclopropanes in high yields. This method was applicable to 1,3-cyclopentanedione, 1,3-indanedione and acyclic 1,3-diones, affording the corresponding cyclopropanes in high yields. In addition, a one-pot synthesis of tetrahydroindol-4(5*H*)-one from 1,3-cyclohexanedione was achieved by exploiting the present protocol and a sequential ring-opening cyclization of spirocyclopropane with benzylamine. Further application of a one-pot reaction to the synthesis of biologically active indole alkaloids is currently in progress.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://….

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11. Typical procedure for the synthesis of cyclohexane-1,3-dione-2-spirocyclopropanes **3** with sulfonium salts **7**: 1-Phenylspiro[2.5]octane-4,8-dione (**3a**) (Table 1, entry 11). Powdered K_2CO_3 (207 mg, 1.5 mmol) and 1,3-cyclohexanedione (**1a**) (56 mg, 0.5 mmol) were added to a suspension of (2-bromo-1-phenylethyl)dimethylsulfonium bromide (**7a**) (245 mg, 0.75 mmol) in EtOAc (5 mL). After stirring at room temperature for 1 h, the reaction mixture was filtered through a Celite pad and the filter cake was rinsed with EtOAc (30 mL). Combined filtrates were washed with water (10 mL) and the aqueous layer was extracted with EtOAc (10 mL x 2). The combined organic layer was washed with brine (10 mL) and dried over anhydrous $MgSO_4$. The filtrate was concentrated in vacuo, and the crude product was purified by column chromatography (silica gel, 25% EtOAc in hexane) to provide **3a** (98 mg, 92%) as a white solid.
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15. Determined by ^1H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard.
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